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REVIEW ARTICLE

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Major relationships among nutrology, gut microbiota and lifestyle change in healthy longevity: a systematic review

Mateus Antunes Nogueira[1*], Hugo Menezes Lopes[2], Márcia Cavalheiro Alves[3], Ricardo de Oliveira Carvalho[4], Ana Claudia Santana Cano[5], Vittor Cândido Soares[6], Frederico Teixeira Izidorio[7], Juliana da Silva Pereira[8], Marília de Andrade Salvá[9], Thamyres Veras Alves[10]

[1] Active Life Teaching and Research (Vida Ativa Ensino e Pesquisa). Street: Paes Leme, 215, conjunto 307, Zip code: 05424-150, Pinheiros, São Paulo, Brazil.
[2] Nossa Senhora das Graças Hospital. Street: Visconde de Jequitinhonha, 1144, Boa Viagem, Recife, Pernambuco, Brazil.
[3] Diagnosis Medical Imaging Clinic Setor C North CNC 1 s/n Lots 10/11. Taguatinga. Brasília, Distrito Federal, Brazil.
[4] University Hospital-UFPI University Campus Minister Petrônio Portela, s/n - Ininga, Teresina, Piauí, Brazil.
[5] Auxiliadora Hospital. Avenue Rosario Congro, 1533, Colinos, Três Lagoas, Mato Grosso do Sul, Brazil.
[6] Hospital da Mulher Mãe Luzia. Obstetric ICU. Avenue Fab, 81 - Central, Macapá, Amapá, Brazil.
[7] Araxá emergency care unit. Av João Paulo II, 1900. Araxá, Minas Gerais, Brazil.
[8] Livia Hasegawa Clinic. Street: Manoel da Nobrega, 354, cj 16 Paraiso, São Paulo, Brazil.
[9] Medradius Oncological Hospital. Street: Hugo Corrêa Paes, 104, Gruta de Lourdes, Maceió, Alagoas, Brazil.
[10] Pelopidas Silveira Hospital, 232, km 6, Curado, Recife, Pernambuco, Brazil.

*Corresponding author: Dr. Mateus Antunes Nogueira.
Active Life Teaching and Research (Vida Ativa Ensino e Pesquisa).
Street: Paes Leme, 215, conjunto 307, Zip code: 05424-150,
Pinheiros, São Paulo, Brazil.
E-mail: hugo_mlopes@hotmail.com

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Abstract

Introduction: In the healthy longevity scenario, individuals over 65 and over 80 years old will be the fastest growing segment of the population. This is associated with the intensification of chronic diseases, such as cardiovascular diseases, diabetes, cancer, sarcopenia, and degenerative diseases (non-communicable diseases). Genetic, epigenetic, and lifestyle factors can determine the longevity of humans. Certain healthy foods are associated with longer telomere lengths. **Objective:** To describe, through a systematic literature review, the main relationships between nutrology, gut microbiota, and lifestyle changes in healthy longevity. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was carried out from May to July 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** 139 articles were found. A total of 51 articles were fully assessed and 22 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies with a high risk of bias and 32 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with X^2 =77.5%>50%. It was concluded that nutrients that can modulate epigenetic pathways, positively influence the outcomes associated with healthy longevity. Studies have shown that the gut microbiota in longlived individuals has a high capacity for lipid metabolism, amino acid degradation, and potential signs of a chronic inflammatory state. Probiotics and prebiotics may be effective alternatives, considering the relationship between the microbiome and healthy aging. Furthermore, resveratrol can modulate epigenetic pathways and may affect outcomes associated with aging, exerting favorable metabolic changes, such as reductions in inflammatory markers or low-density lipoprotein. Nutrients and

natural substances of human physiology and biochemistry such as melatonin, coenzyme Q10, and selenium control the functions of the immune and metabolic systems. Many metabolic or chronic diseases have been implicated in poor diet and lifestyle. Improving the quality of diet is associated with reduced mortality from all causes, whereas multivitamin and multimineral supplements can improve life expectancy.

Keywords: Nutrology. Healthy longevity. Gut microbiota. Nutrients. Lifestyle.

Introduction

In the healthy longevity scenario, individuals aged over 65 and over 80 will be the fastest-growing segment of the population. This is associated with the intensification of chronic diseases such as cardiovascular disease, diabetes, cancer, sarcopenia, and degenerative diseases, which are grouped into so-called non-communicable diseases **[1]**.

In this context, genetic, environmental (epigenetic), and lifestyle factors can determine the longevity of humans **[1]**. Several studies show that nutrition also has the potential to optimize healthy longevity. In humans, certain healthy foods are associated with longer telomere lengths. In addition, a high intake of whole grains, vegetables, fruits, nuts, and also coffee is associated with a reduced risk of all-cause mortality, while a high intake of red meat especially processed meat is positively related to all-cause mortality **[2]**.

In addition, Mediterranean and high-quality diets are associated with a reduced risk of all-cause mortality **[3]**. In this sense, the genetic influence on human life expectancy has been estimated at around 20% to 25%, increasing slightly after the age of 60 **[4]**. However, the main part of healthy aging is determined by lifestyle and environmental factors. In recent decades, improvements in income, nutrition, education, and especially hygiene, medical therapy, and health care have resulted in a significant increase in life expectancy for adults of all ages **[1,5]**.

The factors that are associated with longevity in the populations of Sardinia (Italy), Okinawa (Japan), and Loma Linda (California, USA) are abstinence from smoking, regular physical activity, social engagement and purposeful living, spirituality, maintenance of normal body mass, and related to the last point with a healthy diet with a high consumption of vegetables, fruits, and whole grains **[6]**. Furthermore, eating in moderation, i.e., smaller meals with lower calorie intake, also plays a prominent role in aging, as per the Confucian teaching "hara hachi bu" which means "eat until you are only 80% full" **[7]**.

Given this, preventive measures can radically change individuals' daily habits, including lifestyle-related behaviors **[2,3]**. In this regard, for example, in the context of the COVID-19 pandemic, staying and working from home can affect diet, food choices, and access to food, thus reducing the possibilities and limiting the practice of physical activity **[8,9]**. Thus, sedentary lifestyle and obesity have been described as a global public health problem **[9-11]**. Furthermore, reduced physical activity and lower energy expenditure can negatively affect physical and mental health **[12,13]**. In addition, the pandemic situation is also associated with emotions, such as fear, sadness, and anxiety, which have been shown to reduce sleep quality **[14]**.

In particular, dietary supplementation with coenzyme Q10 (ubiquinone), selenium, melatonin, ascorbic acid (vitamin C), vitamin D, minerals, short-chain fatty acids and omega-3 fatty acids, protein and carbohydrate content, Mediterranean diet and high-fiber diet may be beneficial in strengthening the immune response to fight infections and accelerating cellular apoptosis (with increased cell viability), reducing inflammatory processes and worsening comorbidities such as hypertension, diabetes, obesity, chronic lung disease, heart, liver and kidney disease, tumors, clinically apparent immunodeficiencies, immunodeficiencies such as early secretion capacity of type I interferon and pregnancy **[15]**.

The role of nutrition in mental health is becoming increasingly recognized. Nutrition can be obtained from nutritional supplements such as polyunsaturated fatty acids (PUFA), vitamins, minerals, antioxidants, amino acids, and pre/probiotic supplements **[16]**. A large number of meta-analyses have emerged examining nutritional supplements in the treatment of mental disorders. The strongest scientific evidence was found for PUFAs (mainly eicosapentaenoic acid) as an adjunctive treatment for depression **[16-19]**.

Therefore, the present study described through a systematic review of the literature the main relationships between nutrology, intestinal microbiota, and lifestyle changes in healthy longevity.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-

analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 06/10/2024. The AMSTAR 2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 06/10/2024.

Search Strategy and Search Sources

The literature search process was carried out from May to July 2024 and developed based on Web of Science, Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors in health sciences (DeCS/MeSH Terms) were used: "Nutrology. Healthy longevity. Gut microbiota. Nutrients. Lifestyle" and using the Boolean "and" between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

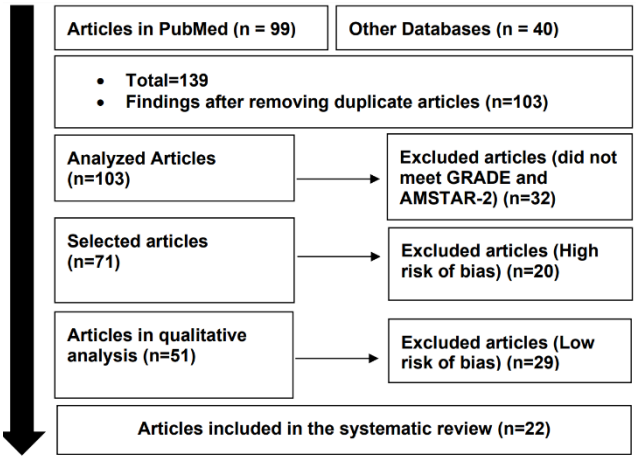
The quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's d test.

Results and Discussion

Summary of Findings

As a corollary of the literature search system, a total of 139 articles were found that were submitted to eligibility analysis and, subsequently, 22 final studies were selected, out of a total of 30, to compose the results of this systematic review. The studies listed presented medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=77.5%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies with a high risk of bias and 32 studies that did not meet GRADE and AMSTAR-2.

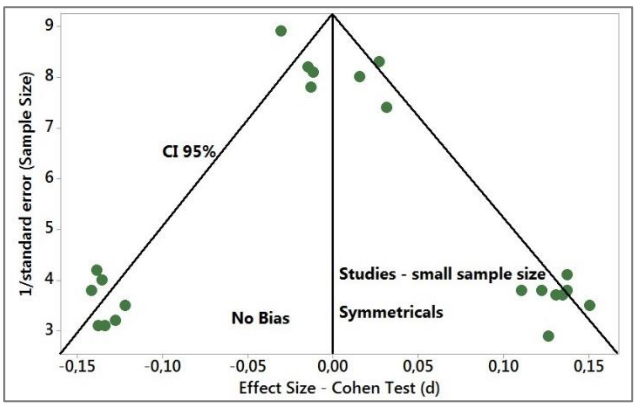
Figure 1. Flowchart showing the article selection process.



Source: Own Authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the bottom of the graph and in studies with large sample sizes that are shown at the top.

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. Studies with high confidence and high recommendation are shown above the graph (n = 22 studies).



Source: Own Authorship.

Nutrologia, Microbiota Intestinal e Estilo de Vida na Longevidade Saudável

Longevity is influenced by genetic, epigenetic, and lifestyle factors. A study by authors Chulenbayeva et al. (2024) **[20]** analyzed metagenomic sequencing of 40 individuals aged 90 years and older who were

conditionally healthy and active, able to serve themselves, without a history of serious infection and cancer, who had not taken any antimicrobials, including probiotics. A significant increase in the expression of pro-inflammatory cytokines IL-1a, IL-6, 12p70, IP-10, IFNα2, IL-15, TNFa, as well as chemokines MIP-1a/CCL3 and MIP-1b/CCL4, chemokine ligands MCP-3/CCL7, and MDC/CCL22(1c) was found. Participants demonstrated a greater diversity of core microbiota genera and showed a high prevalence of the genera Bacteroides, Clostridium, Escherichia, and Alistipes. On the other hand, there was a decrease in the abundance of the genera Ruminococcus, Fusicatenibacter, and Dorea, as well as the species *Fusicatenibacter saccharivorans*.

Furthermore, functional analysis revealed that the microbiome in the long-lived group has a high capacity for lipid metabolism, amino acid degradation, and potential signs of a chronic inflammatory state. In this sense, the microbiome directly impacts aging through the gastrointestinal system. Cellular senescence is an intrinsic aging process that has been associated with microbial imbalance. With age, cells become senescent in stress response, where they undergo irreversible growth arrest while maintaining high metabolic activity. An accumulation of senescent cells has been associated with several chronic and aging pathologies due to an overexpression of the secretory phenotype of pro-inflammatory cytokines, chemokines, growth factors, proteases, lipids, and extracellular matrix components. In this regard, probiotics and prebiotics may be effective alternatives, considering the relationship between the microbiome and healthy aging **[21]**.

Scientific evidence in clinical studies is being accumulated regarding certain nutrients such as resveratrol that can modulate epigenetic pathways and may affect outcomes associated with aging, exerting favorable metabolic changes, such as reductions in inflammatory markers or low-density lipoprotein, which may reduce the risk of some diseases associated with aging. In addition, a high consumption of whole grains, vegetables, fruits, and nuts is convincingly associated with a reduced risk of all-cause mortality. Furthermore, regarding meta-analyses, coffee, and green tea, which are rich in polyphenolic ingredients, exert beneficial effects on survival **[1,2,4]**.

In this scenario, a somewhat more difficult issue regarding the association between nutrition and longevity is the optimal extent/quantity of human protein intake. Epidemiological studies suggest that diets rich in proteins, especially of animal origin, are associated with increased risk of disease. However, higher protein intake is especially important for older adults to increase muscle mass and strength. Focusing on protein-rich plant foods, such as legumes and vegetables, which contain many other components in addition to proteins, such as secondary plant compounds, complex carbohydrates, and dietary fiber, which can influence cellular and body metabolism, may be a rational solution to dietary advice on the protein issue **[1,15]**. In this regard, concerning nutrition and long and healthy life, based on the currently available evidence and recommendations from major international institutions, it is suggested to adopt a healthy (low-sugar) plantbased diet, with a reduced intake of energy-dense meat and processed meat **[19]**.

Also, the main recommendations of public health entities include healthy eating and physical activity as the main lifestyle factors that impact the development of chronic diseases, such as cardiovascular and metabolic diseases, cancer, and even neurological diseases. Randomized clinical trials have been designed to demonstrate that lifestyle modifications can change the pattern of development and progression of chronic diseases, with nutrition being one of the most impactful factors. Choosing a diet considered healthy, such as the Mediterranean diet, has been shown to have an impact on chronic diseases, cardiovascular risk, and adult life expectancy, mainly due to its anti-inflammatory and antioxidant properties. In addition, a high intake of fiber, fruits, and vegetables, together with a low intake of fat and energy-rich processed foods, contribute to a reduction in inflammation and a more robust immune system **[17-19]**.

In the context of nutritional imbalance and its relationship with body and mind, nutrients of interest for cognitive health include polyunsaturated omega-3 fatty acids, polyphenols, vitamin D, and B vitamins. A review by the Scientific Advisory Committee on Nutrition (SACN) (2018) **[18]** suggested that the evidence is insufficient and inconclusive to support the idea that individual nutrients (vitamins C, E and B vitamins, omega-3s, polyphenols, flavonoids and caffeine) could prevent cognitive decline.

Therefore, it remains to be demonstrated whether these individual nutrients are beneficial in preventing cognitive decline. It is difficult and harmful to assume that a single nutrient can cure all diseases. Therefore, it is prudent to affirm the synergistic relationship of nutrients to influence physiological and cognitive function. For example, it is assumed that fish oils may be beneficial for brain health due to their omega-3 composition, but the evidence for fish oil and omega-3s does not indicate that they would be useful

for preserving cognitive health **[22]**. However, oily fish such as herring, mackerel, salmon, trout, and fresh tuna contain omega-3s as well as vitamin D, which may also maintain brain health and mediate cognitive decline. Low vitamin D levels have been associated with accelerated cognitive decline across ethnicities. However, the efficacy of vitamin D supplements rather than dietary sources or sunlight exposure for vitamin D has yet to be demonstrated **[22,23]**.

Instead of individual nutrients, foods that contain these nutrients for cognitive health could also benefit overall health and include fish, fruits, and vegetables **[24]**. Indeed, potentially shifting the focus to whole foods rather than individual nutrients would make recommendations more meaningful. In this scenario, dietary regimens have been suggested as interventions to treat conditions such as hypertension, and dyslipidemia, the Mediterranean diet for metabolic syndrome and cardiovascular health, and the Okinawa diet for healthy aging **[25]**.

In addition, the Mediterranean diet has been offered as a defense against health problems and as a means to healthy aging and cognitive health. It is characterized by high intakes of extra virgin olive oil, vegetables including green leafy vegetables, fruits, whole grains, nuts, pulses, legumes, fish, dairy products, red wine, and low intakes of eggs and confectionery. Numerous scores are available to measure adherence to the Mediterranean diet, but there is limited consensus on scoring criteria in studies, despite it being a useful tool for identifying dietary patterns **[24]**. In this regard, Trichopoulou et al (1995) **[26]** derived the first Mediterranean diet adherence score from the dietary patterns of elderly people in three Greek villages, which positively reflected life expectancy. However, Panagiotakos et al (2006) **[27]** derived their Mediterranean adherence score and compared it with biochemical data, demonstrating that the score was inversely associated with systolic blood pressure, C-reactive protein, total serum cholesterol, and oxidized low-density lipoproteins. Furthermore, greater adherence to the Mediterranean diet has been associated with reduced risk of cognitive decline and development of Alzheimer's disease. However, although the components of the Mediterranean diet are similar, the amounts and frequencies of consumption are inconsistent across studies and mean adherence scores range from 23% to 88%. Furthermore, most studies use variations in food frequency with different numbers of foods **[28]**.

Moreover, certain amino acids are emerging as promising adjunctive treatments for mind-body balance. Although the evidence is still incipient, N-acetylcysteine in particular (at doses of 2,000 mg/day or higher) has been suggested as potentially effective for reducing depressive symptoms and improving functional recovery in mixed psychiatric samples. Furthermore, significant reductions in total schizophrenia symptoms were observed when using N-acetylcysteine as adjunctive treatment, although with substantial heterogeneity between studies, especially in study duration (indeed, Nacetylcysteine has a very late onset of action of about 6 months **[29]**.

N-acetylcysteine acts as a precursor to glutathione, the major endogenous antioxidant, neutralizing cellular reactive oxygen and nitrogen. Glutathione production in astrocytes is limited by cysteine. Oral glutathione and L-cysteine are broken down by first-pass metabolism and do not increase brain glutathione levels, unlike oral Nacetylcysteine, which is more readily absorbed and has been shown to increase brain glutathione in animal models. Furthermore, N-acetylcysteine has been shown to increase dopamine release in animal models **[30]**.

Although there are potential beneficial effects of nutritional supplementation, this should not replace dietary improvement. Improving diet quality is associated with reduced all-cause mortality, whereas multivitamin and multimineral supplements may improve life expectancy **[3,4]**.

In addition, relative energy deficiency syndrome in sport (RED-S) is a clinical entity characterized by low energy availability that can negatively impact the health and performance of male and female athletes. The underlying mechanism of RED-S is an inadequacy of dietary energy to support optimal health and performance. This syndrome refers to impaired physiological function, including metabolic rate, menstrual function, bone health, immunity, protein synthesis, and cardiovascular health, with psychological consequences that may precede (through restrictive dietary habits) or result from RED-S **[11,12]**.

Finally, the benefits of physical activity have drawn increased attention to its physiological effects on the body, including well-being and longevity. The endocannabinoid system (ECS) has emerged as a focal point for determining the mechanisms of how exercise benefits the body and how it reduces or manages pain. The ECS, its ligands [endocannabinoids (eCB)], receptors (CB1 and CB2), enzymes for eCB synthesis and degradation, and the polyunsaturated fatty acids that serve as substrates, comprise a powerful biological organization of multiple controls that affect mood, inflammation, pain, and other neurological aspects of the central and peripheral nervous systems.

Increases in circulating eCB levels have been reported following exercise, with some eCBs exerting analgesic effects from exercise. Future research on the ECS should include mechanistic approaches to endocannabinoid signaling and explain the role of dietary polyunsaturated fatty acids in altering receptor signaling that affects pain. Furthermore, as other types of exercise, such as Tai Chi, have been reported to improve well-being, they should be investigated to see whether changes in eCB mediate the mindbody benefits of Tai Chi **[11]**.

Conclusion

It was concluded that nutrients that can modulate epigenetic pathways, positively influence the outcomes associated with healthy longevity. Studies have shown that the intestinal microbiota in long-lived individuals has a high capacity for lipid metabolism, amino acid degradation, and potential signs of a chronic inflammatory state. Probiotics and prebiotics may be effective alternatives, considering the relationship between the microbiome and healthy aging. Furthermore, resveratrol can modulate epigenetic pathways and may affect outcomes associated with aging, exerting favorable metabolic changes, such as reductions in inflammatory markers or low-density lipoprotein. Nutrients and natural substances of human physiology and biochemistry such as melatonin, coenzyme Q10, and selenium control the functions of the immune and metabolic systems. Many metabolic or chronic diseases have been implicated in poor diet and lifestyle. Improving diet quality is associated with reduced all-cause mortality, whereas multivitamin and multimineral supplements can improve life expectancy.

CRediT

Author contributions: **Conceptualization -** Mateus Antunes Nogueira, Hugo Menezes Lopes, Márcia Cavalheiro Alves; **Data curation -** Ricardo de Oliveira Carvalho, Ana Claudia Santana Cano, Vittor Cândido Soares, Frederico Teixeira Izidorio, Juliana da Silva Pereira, Marília de Andrade Salvá, Thamyres Veras Alves; **Formal Analysis -** Mateus Antunes Nogueira; **Investigation -** Márcia Cavalheiro Alves, Ricardo de Oliveira Carvalho, Ana Claudia Santana Cano, Vittor Cândido Soares, Frederico Teixeira Izidorio, Juliana da Silva Pereira, Marília de Andrade Salvá, Thamyres Veras Alves; **Methodology -** Marília de Andrade Salvá; **Project administration -** Mateus Antunes Nogueira; **Supervision -** Ana Claudia Santana Cano, Vittor Cândido Soares, Frederico Teixeira Izidorio, Juliana da Silva Pereira, Marília de Andrade Salvá, Thamyres Veras Alves; **Writing - original draft -** Mateus Antunes Nogueira, Hugo Menezes Lopes, Márcia Cavalheiro Alves; **Writing-review & editing-** Mateus Antunes Nogueira, Ricardo de Oliveira Carvalho, Ana Claudia Santana Cano, Vittor Cândido Soares, Frederico Teixeira Izidorio, Juliana da Silva Pereira, Marília de Andrade Salvá, Thamyres Veras Alves.

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No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

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